

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application:

Claims 1-37 (cancelled)

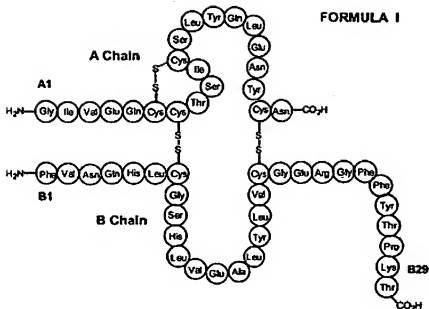
Claim 38 (previously presented): A purified insulin derivative comprising an insulin molecule and a single reactive group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain and the reactive group being a maleimido-containing group, wherein the reactive group is coupled to an amino group of the N-terminus amino acid of the B chain of the insulin molecule.

Claims 39-40 (cancelled)

Claim 41 (previously presented): The insulin derivative of claim 38, wherein the α -amino group is the α -amino group of Phe B1.

Claim 42 (previously presented): The insulin derivative of claim 38, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

Claim 43 (previously presented): The insulin derivative of claim 38, wherein the insulin molecule is of formula I:



and the reactive group is coupled to an amino acid of the insulin molecule at a position Phe B1 of the insulin molecule.

Claim 44 (cancelled)

Claim 45 (previously presented): The insulin derivative of claim 38, wherein the reactive group coupled to the α -amino group of the insulin molecule is:



Claim 46 (previously presented): The insulin derivative of claim 41, wherein the reactive group coupled to the α -amino group of the insulin molecule is:



Claim 47 (cancelled)

Claim 48 (previously presented): The insulin derivative of claim 38, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 49 (previously presented): The insulin derivative of claim 41, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 50 (previously presented): The insulin derivative of claim 46, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 51 (previously presented): The insulin derivative of claim 45, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

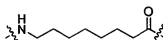
Claim 52 (previously presented): The insulin derivative of claim 48, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$ where n is an integer between 1 and 20.

Claim 53 (previously presented): The insulin derivative of claim 49, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$ where n is an integer between 1 and 20.

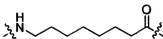
Claim 54 (previously presented): The insulin derivative of claim 50, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$ where n is an integer between 1 and 20.

Claim 55 (previously presented): The insulin derivative of claim 51, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy]] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

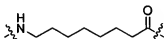
Claim 56 (previously presented): The insulin derivative of claim 48, wherein the linker is:



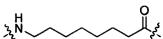
Claim 57 (previously presented): The insulin derivative of claim 49, wherein the linker is:



Claim 58 (previously presented): The insulin derivative of claim 50, wherein the linker is:



Claim 59 (previously presented): The insulin derivative of claim 51, wherein the linker is:



Claim 60 (cancelled)

Claim 61 (previously presented): The insulin derivative of claim 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

Claim 62 (previously presented): The insulin derivative of claim 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropanylcarbonyl)aminooctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropanylcarbonyl)aminooctanamide.

Claim 63 (cancelled)

Claim 64 (cancelled)

Claim 65 (previously presented): The insulin derivative of claim 38, wherein the albumin is recombinant albumin.

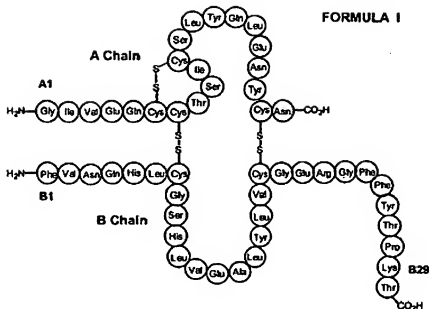
Claim 66 (previously presented): An insulin conjugate comprising an insulin molecule, a reactive group and an albumin, the insulin molecule comprises an A chain and a B chain and the reactive group is a maleimido-containing group, wherein the reactive group is coupled to an α -amino group of the N-terminus amino acid of the B chain of the insulin and wherein the reactive group is covalently bonded to the albumin.

Claims 67-68 (cancelled)

Claim 69 (previously presented): The insulin conjugate of claim 66, wherein the α -amino group is the α -amino group of Phe B1.

Claim 70 (previously presented): The insulin conjugate of claim 66, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

Claim 71 (previously presented): The insulin conjugate of claim 66, wherein the insulin molecule is of formula I:



and the reactive group is coupled to the α -amino group of Phe B1 of the insulin molecule.

Claim 72 (cancelled)

Claim 73 (previously presented): The insulin conjugate of claim 66, wherein the reactive group coupled to the α -amino group of the insulin molecule is:



Claim 74 (previously presented): The insulin conjugate of claim 69, wherein the reactive group coupled to the α -amino group of the insulin molecule is:



Claim 75 (cancelled)

Claim 76 (previously presented): The insulin conjugate of claim 66, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 77 (previously presented): The insulin conjugate of claim 69, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 78 (previously presented): The insulin conjugate of claim 74, wherein the reactive group is coupled to the α -amino group of the insulin molecule via a linker.

Claim 79 (previously presented): The insulin conjugate of claim 73, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

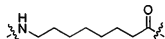
Claim 80 (previously presented): The insulin conjugate of claim 76, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

Claim 81 (previously presented): The insulin conjugate of claim 77, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

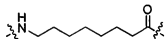
Claim 82 (previously presented): The insulin conjugate of claim 78, wherein the reactive group is coupled to the α -amino group of the insulin molecule by reacting a linker with the reactive group and the α -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

Claim 83 (previously presented): The insulin conjugate of claim 79, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino)ethoxy]ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$ where n is an integer between 1 and 20.

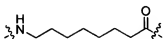
Claim 84 (previously presented): The insulin conjugate of claim 76, wherein the linker is:



Claim 85 (previously presented): The insulin conjugate of claim 77, wherein the linker is:



Claim 86 (previously presented): The insulin conjugate of claim 78, wherein the linker is:



Claims 87-88 (cancelled)

Claim 89 (previously presented): The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

Claim 90 (previously presented): The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropylcarbonyl)aminooctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropylcarbonyl)aminooctanamide.

Claims 91-92 (cancelled)

Claim 93 (previously presented): The insulin conjugate of claim 66, wherein the albumin is recombinant albumin.

Claims 94-115 (cancelled)

Claim 116 (previously presented): A pharmaceutical composition comprising an insulin derivative of claim 38 and a pharmaceutically acceptable carrier.

Claim 117 (previously presented): A pharmaceutical composition comprising an insulin conjugate of claim 66 and a pharmaceutically acceptable carrier.

Claim 118 (previously presented): A method of treating a glycaemic-related disease in a subject, comprising:

administering to the subject an insulin derivative of claim 38, to thereby treat the glycaemic related disorder.

Claim 119 (previously presented): The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

Claim 120 (previously presented): The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

Claim 121 (previously presented): A method of treating a glycaemic-related disease in a subject, comprising:

administering to the subject an insulin conjugate of claim 66, to thereby treat the glycaemic related disorder.

Claim 122 (previously presented): The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

Claim 123 (previously presented): The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

Claim 124 (previously presented): A method of making the conjugate of claim 66 in vivo in a subject, the method comprising administering to a subject an insulin derivative of claim 38, wherein a covalent bond between the reactive group of the insulin derivative and the albumin is formed in the subject.

Claims 125-130 (cancelled)

Claim 131 (previously presented): The insulin derivative of claim 41, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.

Claim 132 (previously presented): The insulin derivative of claim 38, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.

Claim 133 (previously presented): A pure fraction of an insulin derivative comprising an insulin molecule connected with or without a linker to a single a maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an amino group of the N-terminus amino acid of the B chain of the insulin molecule.

Claim 134 (new): The insulin conjugate of claim 66, wherein the albumin is serum albumin.

Claim 135 (new): The insulin conjugate of claim 90, wherein the albumin is serum albumin.

Claim 136 (new): The insulin conjugate of claim 90, wherein the albumin is recombinant albumin.

Claim 137 (new): A pharmaceutical composition comprising an insulin conjugate of claim 90 and a pharmaceutically acceptable carrier.

Claim 138 (new): A method of treating a glycaemic-related disease in a subject, comprising:

administering to the subject an insulin conjugate of claim 90, to thereby treat the glycaemic related disorder.

Claim 139 (new): The method of claim 138, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.